

MEMORANDUM

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

PID#: D040141

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SUBJECT: One Year Post-Pediatric Exclusivity Postmarketing Adverse Event Review: Drug Use Data
Rofecoxib (Vioxx®, NDA 21-042, NDA 21-052)
Pediatric Exclusivity Grant Date: February 18, 2004

****This document contains proprietary data from IMS Health which cannot be shared outside of FDA without clearance from IMS Health obtained through the Office of Drug Safety.****

EXECUTIVE SUMMARY

This consult examines use of rofecoxib in the pediatric population (0-16 years), with primary focus on patterns of use one year before and one year following the granting of Pediatric Exclusivity on February 18, 2004. Rofecoxib, trade name Vioxx®, was withdrawn from the market on September 30, 2004, by its manufacturer Merck after receiving reports of increased cardiovascular risk from the APPROVe trial (see NEJM 2005; 352:1092-1102). Proprietary drug use databases licensed by the Food and Drug Administration (henceforth referred to as the “Agency”) were used to conduct this analysis. The IMS Health, National Sales Perspectives™ was used to determine the various retail and non-retail channels of distribution. Since the majority of use for this product occurs in the outpatient setting, we further examined the

utilization patterns for rofecoxib focusing on the outpatient setting. Outpatient use was measured by two IMS Health audits, the National Prescription Audit *Plus*TM (NPA *Plus*TM) and the National Disease and Therapeutic IndexTM (NDTITM).

We examined prescriptions dispensed for rofecoxib as well as for other selective COX-2 inhibitors (e.g., celecoxib and valdecoxib) to compare rofecoxib use to other products in the same therapeutic class.

There was an overall decrease in the estimated number of prescriptions dispensed for the COX-2 inhibitor class of drugs from 53.9 million prescriptions in year 2003 to 50.7 million prescriptions dispensed in year 2004 (5.8% decrease). Celecoxib (Celebrex®) led the market in all the years studied, followed by rofecoxib (Vioxx®) and valdecoxib (Bextra®). During the two years prior to the granting of pediatric exclusivity, rofecoxib held approximately 37.0% - 41.4% of the COX-2 market share. During the first nine months of year 2004 before the withdrawal of Vioxx® on September 30, 2004, the market share for this class of compounds shifted slightly from the previous year with 34% for Vioxx® (decrease from 37% in year 2003), 43% for Celebrex® (stable at 44% in year 2003) and 23% for Bextra® (increase from 19% in year 2003)¹. The 2004 total year market share for Vioxx® declined to 27.6% of the overall COX-2 market.

The 25 mg tablet strength of rofecoxib was the most commonly dispensed dosage strength for all 3 years analyzed. In 2004, for example, approximately 81% of dispensed rofecoxib prescriptions were for the 25 mg strength, followed by 10% for the 50 mg strength and 9% for the 12.5 mg strength. The oral suspension dosage form of rofecoxib represented less than 1% of the overall rofecoxib dispensing.

The most common prescribing specialties for Vioxx® in year 2003 were Internal Medicine (25%), Family Practice (22%), and Orthopedic Surgery (11%). Together, these specialties accounted for nearly 60% of the dispensed prescriptions for Vioxx® in year 2003. Pediatricians were responsible for less than 1% of dispensed prescriptions for Vioxx®. In general, prescribing patterns for this product showed relatively little change across provider specialties from year 2000 - 2004.

During years 2002 through 2004, less than 1.5% of drug mentions for Vioxx® were associated with the pediatric population (ages 0-16 years). The preponderance of use within this group appeared in children ages 12-16 years (86% - 91%). Slightly more than half of all pediatric mentions of Vioxx® during office-based physician visits were among females (56%) during the 3-year study time period. A similar pattern was observed in adults.

Since IMS Health, NPA *Plus*TM does not include demographic information on patients for the entire time period of interest, we applied the proportions for demographic subgroups from IMS Health, NDTITM to IMS Health, NPA *Plus*TM data in an effort to approximate the number of prescriptions dispensed for Vioxx® nationwide to children. Using this approach, approximately

¹ IMS Health, National Prescription Audit *Plus*TM, Months January – September 2004, Extracted May 2005.
File: NPA Governale 5-27-05 D040141 COX2 1st 9 mos 2004 TRx 05059mos.xls

200,000 prescriptions for Vioxx® are estimated to have been dispensed for persons aged 1-16 years in the U.S. during year 2003.

According to IMS Health, NDTI™, the diagnosis, or indication, most frequently linked to Vioxx® use in the pediatric population (0-16 years) during year 2004 was “pain in joint” (ICD-9 code 719.4), accounting for almost 16% of the total Vioxx® mentions during office-based physicians visits. In the adult population (17 years and over), “osteoarthritis, unspecified” represented the greatest percentage of use at 14.3%.

Overall, the use of the COX-2 inhibitors, rofecoxib and celecoxib, began declining before the market withdrawal of rofecoxib. Celecoxib use increased slightly in year 2004, relative to year 2003. The withdrawal of Vioxx® from the market in September 2004 and the intense scrutiny on this class of drugs that followed may have had an effect on the use of COX-2 products.

INTRODUCTION

On January 3, 2001, Congress enacted the Best Pharmaceuticals for Children Act (BPCA) to improve the safety and efficacy of pharmaceuticals for children. Section 17 of that act requires the reporting of adverse events associated with the use of a drug in children during the one year following the date on which the drug received marketing exclusivity. In support of this mandate, the FDA is required to provide a report to the Pediatric Advisory Committee on the drug utilization patterns and adverse events associated with the use of the drug on a quarterly basis. This review is in addition to the routine post-marketing safety surveillance activities the FDA performs for all marketed drugs.

Vioxx® (rofecoxib), an orally active cyclooxygenase-2 (COX-2) inhibitor, was approved on May 20, 1999, for the relief of the signs and symptoms of osteoarthritis (OA), the management of acute pain in adults, and the treatment of primary dysmenorrhea. On April 11, 2002, Vioxx was approved for the relief of the signs and symptoms of rheumatoid arthritis (RA) in adults. On March 26, 2004, it received an additional indication for the treatment of acute migraine attacks with or without aura in adults (NDA 21-647).

The Pediatric Exclusivity Board of the FDA granted pediatric exclusivity for Vioxx® Tablets and Oral Suspension (NDA 21-042, NDA 21-052) on February 18, 2004. On August 20, 2004, Vioxx® was approved for use in patients 2 years to 17 years of age for the treatment of the signs and symptoms of pauciarticular and polyarticular juvenile rheumatoid arthritis (JRA) to NDAs 21-042 (Tablets 12.5 mg and 25 mg) and 21-052 (Oral Suspension 12.5 mg/mL and 25 mg/mL).

A little over a month after the approval of the pediatric indication, Vioxx® was withdrawn from the market on September 30, 2004, by its manufacturer, Merck, after receiving reports of increased cardiovascular risk from the APPROVe trial (see NEJM 2005; 352:1092-1102). This review describes outpatient drug use patterns for Vioxx® in the pediatric population as well as in the adult population in the years prior to and subsequent to the granting of pediatric exclusivity

and the removal of the product from the market on September 30, 2004. Because of the withdrawal of the product, we were only able to examine seven months of use after the granting of pediatric exclusivity, rather than the customary one year of use. Proprietary drug use databases licensed by the Agency were used to conduct this analysis.

METHODS

IMS Health, National Sales Perspectives™ data were used to determine the setting in which the product was sold. Sales of this product by number of tablets sold from the manufacturer to various retail and non-retail channels of distribution were analyzed (data not shown). Since the majority of use for this product occurs in the outpatient setting (88.5% of all tablets and oral suspension sold were to outpatient pharmacies during year 2003), we further examined the utilization patterns for rofecoxib focusing on the outpatient setting only. Outpatient use was measured by two IMS Health audits, the National Prescription Audit *Plus*™ (NPA *Plus*™) and the National Disease and Therapeutic Index™ (NDTI™).

We examined prescriptions dispensed for Vioxx® as well as other COX-2 inhibitors to compare Vioxx® use relative to other products of the same therapeutic class. Other COX-2 inhibitors included in this analysis are Celebrex® and Bextra®.

DATA SOURCES - OUTPATIENT DRUG USE

IMS HEALTH, NATIONAL PRESCRIPTION AUDIT PLUS™ (NPA PLUS™)

NPA Plus™ measures the retail dispensing of prescriptions, or the frequency with which drugs move out of retail pharmacies into the hands of consumers via formal prescriptions. These retail pharmacies include chain, independent, food store, mail order, discount houses, and mass merchandiser pharmacies, as well as nursing home (long-term care) pharmacy providers. Information on the specialty of the prescribing physician can also be collected, except for in the long-term care and mail order pharmacy settings.

The number of dispensed prescriptions is obtained from a sample of approximately 22,000 pharmacies throughout the U.S. and projected nationally. The pharmacies in the database account for approximately 40% of all pharmacy stores and represent approximately 45% of prescription coverage in the U.S.

Data for this analysis include total prescriptions dispensed for Vioxx® and other COX-2 inhibitors from January 1, 2002, through December 31, 2004. Data for Vioxx® only includes up to September 30, 2004.

IMS HEALTH, NATIONAL DISEASE AND THERAPEUTIC INDEX™ (NDTI™)

The National Disease and Therapeutic Index™ (NDTI™) is an ongoing survey designed and conducted by IMS Health to provide descriptive information on the patterns and treatment of disease encountered in office-based practice in the continental U.S. The data are collected

from a panel of roughly 2,000 – 3,000 office-based physicians who complete and submit a survey of their practice patterns to IMS Health for two consecutive days per quarter. These data may include profiles and trends of diagnoses, patients, drug products mentioned and treatment patterns. The data are projected nationally to reflect national prescribing patterns.

NDTI™ uses the term “appearances” and “uses” for drug reports. A drug appearance roughly translates to a mention of a drug during a patient visit, unduplicated by the number of diagnoses for which it may be used. A drug appearance can result from a prescription written, a refill authorized, a sample given, the drug administered in the office, etc., or any combination of these. For example, a patient receiving a sample of a drug and also a prescription for that same drug for two different indications will be counted as one drug “appearance.” On the other hand, NDTI™ also uses the term “uses” for mentions of a drug in association with a diagnosis during a patient visit. This term may be duplicated by the number of diagnosis for which the drug is mentioned. Due to the differences in definitions for these measures, the counts may vary slightly from one another for the same attribute, such as gender or age. However, the differences observed between these measures are not likely to be substantial. It is important to note that drug appearances and drug use do not necessarily result in a prescription being generated. Rather, the term indicates that a given drug was mentioned during an office visit.

For this analysis, we examined annual mentions of Vioxx® during office-based physician visits from January 1, 2002, until market withdrawal on September 30, 2004.

RESULTS

I. Dispensed Prescriptions

There was a 5.8% decrease in the estimated number of prescriptions dispensed for the COX-2 inhibitor class of drugs from 53.9 million prescriptions in year 2003 to 50.7 million prescriptions dispensed in year 2004 (Table 1). Celebrex® (celecoxib) led the market in all the years observed, followed by Vioxx® (rofecoxib) and Bextra® (valdecoxib). During the two years prior to the granting of pediatric exclusivity, Vioxx® held approximately 37% - 41% of the COX-2 market share. During the first nine months of year 2004 before the withdrawal of Vioxx® on September 30, 2004, the market share for this class of compounds shifted slightly from the previous year with 34% for Vioxx® (decrease from 37% in year 2003), 43% for Celebrex® (stable at 44% in year 2003) and 23% for Bextra® (increase from 19% in year 2003)². The total year market share for Vioxx® declined to 27.6% of the overall COX-2 market after market withdrawal.

The 25 mg tablet strength of Vioxx® was the most commonly dispensed dosage strength for all 3 years analyzed. In 2004, for example, approximately 81% of dispensed Vioxx® prescriptions were for the 25 mg strength, followed by 10% for the 50 mg strength and 9% for the 12.5 mg

² IMS Health, National Prescription Audit *Plus*™, Months January – September 2004, Extracted May 2005.
File: NPA Governale 5-27-05 D040141 COX2 1st 9 mos 2004 TRx 05059mos.xls

strength. The oral suspension dosage form of Vioxx® held less than 1% of the overall Vioxx® dispensing.

Table 1: Total Number of Prescriptions Dispensed (in thousands) for Vioxx® and other COX-2 Inhibitors in Retail Pharmacies, IMS Health, National Prescription Audit Plus™, 2002 - 2004

	2002		2003		2004*	
	Prescriptions (000)	%	Prescriptions (000)	%	Prescriptions (000)	%
Total COX-2 Inhibitors	53,261	100.0	53,889	100.0	50,743	100.0
Vioxx	22,021	41.4	19,959	37.0	13,994	27.6
Tablets	22,021	99.9	19,929	99.8	13,968	99.8
12.5 mg	2,051	9.3	1,810	9.1	1,209	8.7
25 mg	17,558	79.7	16,013	80.4	11,311	81.0
50 mg	2,412	11.0	2,106	10.6	1,448	10.4
Oral Suspension	23	0.1	30	0.2	26	0.2
12.5 mg/mL	10	52.2	13	56.7	11	57.7
25 mg/mL	12	43.5	17	43.3	15	42.3
Celebrex	26,006	48.8	23,556	43.7	23,893	47.1
Bextra	5,211	9.8	10,374	19.3	12,856	25.3

IMS Health, National Prescription Audit Plus™, Years 2002 - 2004, Extracted January 2005.

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* Vioxx data for year 2004 only includes months January through its market withdrawal in September 2004.

The most common prescribing specialties for Vioxx® in 2003 were Internal Medicine (25%), Family Practice (22%), and Orthopedic Surgery (11%). Together, these specialties accounted for nearly 60% of the dispensed prescriptions for Vioxx®. Pediatricians were responsible for less than 1% of dispensed prescriptions for Vioxx® (Table 2). In general, prescribing patterns for this product showed relatively little change across provider specialties from year 2000 - 2004 (data not shown).

Table 2: Total Number of Prescriptions Dispensed (in thousands) for Vioxx® by Physician Specialty, IMS Health, National Prescription Audit *Plus*™, 2003*

Prescriber Specialty		Prescriptions (000)	%
All prescribers		17,160	100.0
1	Internal Medicine	4,363	25.4
2	Family Practice	3,834	22.3
3	Orthopedic Surgery	1,866	10.9
4	Osteopathic Medicine	1,493	8.7
5	Rheumatology	792	4.6
...			
23	Pediatrics	102	0.6
	Other Specialties (70)	4,710	27.5

IMS Health, National Prescription Audit *Plus*™, Year 2003, Extracted May 2005.

Original file: 0505vio1.dvr

* Excluding Long-Term Care and Mail Order Pharmacies

II. Patient Demographics

During years 2002 through 2004, no more than 1.5% of drug mentions for Vioxx® were associated with the pediatric population (ages 0-16 years) (Table 3). The preponderance of use within this group appeared almost exclusively in children ages 12-16 years (86-91%). Slightly more than half of all mentions of Vioxx® during office-based physician visits were in female children (56%) during the 3-year time period surveyed. A similar pattern was observed in adults.

Table 3: Total Number of Drug Appearances (N) for Vioxx® (in thousands) by age groups and gender during Office-Based Physician Visits, IMS Health, National Disease and Therapeutic Index™, 2002 – 2004

Characteristics	2002		2003		2004 [‡]	
	N (000)	%*	N (000)	%*	N (000)	%*
Age (years)						
TOTAL	11,109	(100.0)	9,717	(100.0)	6,876	(100.0)
0-16	167	(1.5)	104	(1.1)	71	(1.0)
Female	94	(56.1)	56	(53.5)	48	(68.0)
Male	74	(44.0)	49	(46.8)	23	(31.9)
2-5	1	(0.6)	2	(2.3)	8	(10.6)
Female	0	(0.0)	0	(0.0)	8	(100.0)
Male	1	(100.0)	2	(100.0)	0	(0.0)
6-11	14	(8.4)	12	(11.3)	2	(3.4)
Female	10	(68.2)	8	(69.3)	2	(64.2)
Male	5	(32.2)	3	(28.5)	1	(35.8)
12-16	152	(91.1)	90	(86.7)	61	(85.8)
Female	84	(55.3)	47	(52.6)	39	(64.2)
Male	68	(44.8)	43	(47.6)	22	(35.7)
17+	10,942	(98.5)	9,613	(98.9)	6,805	(99.0)
Female	6,095	(55.7)	5,345	(55.6)	3,783	(55.6)
Male	4,847	(44.3)	4,267	(44.4)	3,022	(44.4)

IMS Health, National Disease and Therapeutic Index™, Year 2002 - 2004, Extracted May 2005.

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* Percent in parentheses represents percent of the total number of mentions for Vioxx®

‡ Vioxx data for year 2004 only includes months January through its market withdrawal in September 2004.

§ Figures may not add up to Total due to rounding.

Since IMS Health, NPA Plus™ does not include demographic information on patients for the entire time period of interest, we applied the proportions for demographic subgroups from IMS Health, NDTI™ to IMS Health, NPA Plus™ data in an effort to approximate the number of prescriptions dispensed for Vioxx® nationwide to children. Using this approach, approximately 220,000 prescriptions for Vioxx® are estimated to have been dispensed for persons aged 1-16 years in the U.S. during year 2003 (Table 4).

Table 4: Estimated Nationwide Prescriptions Dispensed for Vioxx® in the Pediatric Age Group (1-16) During Year 2003

Total Number of Prescriptions* Dispensed for All Age Groups (from Table 2)	% Pediatric Claims** (Ages 1-16 yrs) (from Table 3)	Estimated Number of Prescriptions Dispensed to the Pediatric Population (Age 1-16 yrs)
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TOTAL	19,959,000	1.1%	219,549
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*IMS Health, National Prescription Audit *Plus*™, Year 2003, Extracted January 2005.

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**IMS Health, National Disease and Therapeutic Index™, Year 2003, Extracted May 2005.

Original File: 0505COX2 SxAg.dvf

III. Indication for Use

According to IMS Health, NDTI™, the diagnosis, or indication, most frequently linked to Vioxx® use in the pediatric population (0-16 years) during calendar year 2004 was “pain in joint” (ICD-9 code 719.4), accounting for almost 16% of the total Vioxx® mentions during office-based physicians visits (Table 5). In the adult population (17 years and over), “osteoarthritis, unspecified” had the greatest percentage of use with 14.3% followed by other arthritic and painful conditions.

Table 5: Indications Associated with Mentions of Vioxx® (in thousands) During Office-Based Physician Visits by Patient Age Groups, IMS Health, National Disease and Therapeutic Index™, 2002 – 2004

	2002		2003		2004*	
	N (000)	%	N (000)	%	N (000)	%
Vioxx® Total Mentions	11,644	(100.0)	10,184	(100.0)	7,177	(100.0)
Patient Age 0-16	174	(1.5)	108	(1.1)	80	(1.1)
719.4 Pain in joint	8	(4.8)	7	(6.9)	13	(15.9)
716.9 Arthropathy, unspecified	6	(3.7)	2	(1.8)	11	(13.7)
729.1 Myalgia and myositis, unspecified	1	(0.7)	1	(0.8)	9	(11.4)
714.3 Juvenile chronic polyarthritis	2	(1.1)	3	(2.9)	7	(9.1)
717.3 Other and unspecified derangement of medial meniscus	4	(2.1)	4	(3.4)	7	(8.8)
Patient Age 17+	11,470	(98.5)	10,076	(98.9)	7,097	(98.9)
715.9 Osteoarthritis, unspecified whether generalized or localized	1,740	(15.2)	1,629	(16.2)	1,017	(14.3)
716.9 Arthropathy, unspecified	722	(6.3)	487	(4.8)	391	(5.5)
719.4 Pain in joint	555	(4.8)	577	(5.7)	353	(5.0)
724.2 Lumbago	438	(3.8)	357	(3.5)	343	(4.8)
V67.0 Post-Op Surgical Exam	583	(5.1)	555	(5.5)	333	(4.7)

IMS Health, National Disease and Therapeutic Index™, Years 2002 – 2004, Extracted May 2005.

Original File: 0505COX2 AgDx.dvf

* Vioxx data for year 2004 only includes months January through its market withdrawal in September 2004.

DISCUSSION

Based on the databases that were used for this consult, the use of the COX-2 inhibitors, rofecoxib and celecoxib, began declining before the market withdrawal of rofecoxib. Celecoxib use increased slightly in year 2004, relative to year 2003. The withdrawal of Vioxx® from the market in September 2004 and the intense scrutiny on this class of drugs that followed may have had an effect on the use of COX-2 products.

Findings from this consult should be interpreted in the context of the known limitations of the databases used. NPA Plus™ data provide an estimate of the total number of prescriptions dispensed in the U.S. The data, however, do not include historical demographic information, such as age and gender. The inclusion of prescriber specialty data in this report does not include the mail order and long-term care channels.

NDTI™ data provide estimates of patient demographics and indications for use of medicinal products in the U.S. Due to the sampling and data collection methodologies, the small sample size can make these data unstable, particularly when use is not prevalent in the pediatric population. These results should be interpreted with caution. Prior data suggest that approximately 71% of drug mentions result in a prescription, sample or drug administration³. For this analysis, we assumed that all physician-patient contact during an office-visit resulted in a filled prescription for Vioxx®. This assumption was applied when approximating the nationwide number of prescriptions dispensed for Vioxx® to children.

CONCLUSION

There was an overall decrease in the estimated number of prescriptions dispensed for the COX-2 inhibitor class of drugs from 53.9 million prescriptions in year 2003 to 50.7 million prescriptions dispensed in year 2004 (5.8% decrease). During the two years prior to the granting of pediatric exclusivity, Vioxx® held approximately 37.0% - 41.4% of the COX-2 market share. During the first nine months of year 2004 before the withdrawal of Vioxx® on September 30, 2004, the market share for this class of compounds shifted slightly from the previous year with 34% for Vioxx® (decrease from 37% in year 2003), 43% for Celebrex® (stable at 44% in year 2003) and 23% for Bextra® (increase from 19% in year 2003)⁵. The 2004 total year market share for Vioxx® declined to 27.6% of the overall COX-2 market after market withdrawal.

Approximately 81% of dispensed Vioxx® prescriptions were for the 25 mg strength, followed by 10% for the 50 mg strength and 9% for the 12.5 mg strength. The oral suspension dosage form of Vioxx® held less than 1% of the overall Vioxx® dispensing. Pediatricians were responsible for less than 1% of dispensed prescriptions for Vioxx® during each of the three years analyzed.

During years 2002 through 2004, no more than 1.5% of drug mentions for Vioxx® were associated with the pediatric population (ages 0-16 years). The preponderance of use within this group appeared almost exclusively in children ages 12-16 years (86% - 91%). Slightly more than half of all mentions of Vioxx® during office-based physician visits were in female children (56%) than male children (44%) during the 3-year time period surveyed. Using the proportions for demographic subgroups from IMS Health, NDTI™ to IMS Health, NPA Plus™ data, an estimated 220,000 prescriptions for Vioxx® were dispensed to persons aged 1-16 years in the U.S. during year 2003. According to IMS Health, NDTI™, the diagnosis, or indication, most

³ IMS Health, National Disease and Therapeutic Index™, Years 1998 – 2003; File name: NDTI Wysowski 9-28-04 0409 Prod Issued 98-03.xls; Original File: 0409 Prod Issued 98-03.dvf.

⁵ IMS Health, National Prescription Audit Plus™, Months January – September 2004, Extracted May 2005. File: NPA Governale 5-27-05 D040141 COX2 1st 9 mos 2004 TRx 05059mos.xls

frequently linked to Vioxx® use in the pediatric population (0-16 years) during year 2004 was “pain in joint” (ICD-9 code 719.4), accounting for almost 16% of the total Vioxx® mentions during office-based physicians visits.

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